

CLAIMS

1. A method for treating diabetes or diabetes related disease in a subject in need of such treatment, said method comprising administering to said subject an effective amount of an
5 extendin-4 compound and an effective amount of a thiazolidinedione insulin sensitizer.
2. The method according to claim 1, wherein said diabetes or diabetes related disease is selected from the group consisting of type 1 diabetes, type 2 diabetes, hyperglycemia, type 1.5 diabetes, latent autoimmune diabetes in adults, maturity onset diabetes, beta-cell apoptosis,
10 hemochromatosis induced diabetes, impaired glucose tolerance, metabolic syndrome X, insulin resistance, cystic fibrosis related diabetes, polycystic ovarian syndrome, and gestational diabetes.
3. The method according to claim 1, wherein said diabetes or diabetes related disease is selected from the group consisting of obesity, dyslipidemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, hypertension, essential hypertension, acute hypertensive emergency, arteriosclerosis, atherosclerosis, intermittent claudication (atherosclerosis obliterans), cardiovascular disease, cardiomyopathy, cardiac hypertrophy, left ventricular hypertrophy, coronary artery disease, early coronary artery
15 disease, heart insufficiency, exercise tolerance, chronic heart failure, mild chronic heart failure, arrhythmia, cardiac dysrhythmia, syncope, heart attack, myocardial infarction, Q-wave myocardial infarction, stroke, acute coronary syndrome, angina pectoris, unstable angina, cardiac bypass reocclusion, diastolic dysfunction, systolic dysfunction, non-Q-wave cardiac necrosis, catabolic changes after surgery, acute pancreatitis, and irritable bowel syndrome.
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4. The method according to claim 1, wherein said diabetes or diabetes related disease is selected from the group consisting of diabetic retinopathy, background retinopathy, preproliferative retinopathy, proliferative retinopathy, macular edema, cataracts, nephropathy, diabetic nephropathy, microalbuminuria, macroalbuminuria, neuropathy, diabetic neuropathy, distal
25 symmetrical sensorimotor polyneuropathy, and diabetic autonomic neuropathy.
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5. The method according to claim 1, wherein said extendin-4 compound is selected from the group consisting of extendin-4, an extendin-4 analogue, an extendin-4 derivative, an extendin-4 fusion protein, a DPPIV protected extendin-4, and an immunomodulated extendin-4 .
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6. The method according to claim 1, wherein said exendin-4 compound has a binding affinity towards the GLP-1 receptor which is at least ten fold higher than that of GLP-1(7-37).
7. The method according to claim 1, wherein said exendin-4 compound has a binding affinity
5 towards the GLP-1 receptor which is at least 100 fold higher than that of GLP-1(7-37).
8. The method according to claim 1, wherein said exendin-4 compound has at least the same affinity towards the GLP-1 receptor as that of exendin-4(1-39).
- 10 9. The method according to claim 1, wherein said exendin-4 compound has at least twice the affinity as that of exendin-4(1-39) towards the GLP-1 receptor as that of exendin-4(1-39).
10. The method according to claim 1, wherein said exendin-4 compound is a fusion protein which comprises exendin-4, an analogue thereof or a derivative of any one of the foregoing,
15 coupled optionally via a spacer to a stabilizing peptide which confers an increased half-life in human serum to said fusion protein as compared to the fusion protein devoid of said spacer and stabilizing peptide.
11. The method according to claim 10, wherein said spacer is selected from the group
20 consisting of a peptide so that said fusion protein can be directly produced by recombinant DNA techniques, a peptide connected in either end in a way that said fusion protein cannot be produced directly by recombinant DNA techniques, a peptide comprising two amino acid residues and a non-peptide moiety.
- 25 12. The method according to claim 1, wherein said exendin-4 compound comprises a sequence of 25 amino acids which are identical to a sequence of 25 amino acids in human serum albumin.
13. The method according to claim 1, wherein said exendin-4 compound comprises a poly-
30 ethylene glycol moiety.
14. The method according to claim 5, wherein said immunomodulated exendin-4 has an immune response in humans which is less than that of exendin-4(1-39), said immune response being measured as the concentration of antibodies reactive to the exendin-4 compound after
35 4 weeks of treatment of the patient.

15. The method according to claim 5, wherein said immunomodulated exendin-4 has an immune response in humans which is less than 20% of the response of exendin-4(1-39), said immune response being measured as the concentration of antibodies reactive to the exendin-4 compound after 4 weeks of treatment of the patient.

16. The method according to claim 1, wherein said thiazolidinedione insulin sensitizer is selected from the group consisting of troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037, T174, and TZD 300512, 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a salt thereof.

17. The method according to claim 1, wherein the exendin-4 compound is exendin-4(1-39) and the thiazolidinedione insulin sensitizer is troglitazone, pioglitazone, 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione, or a salt thereof.

18. The method according to claim 1, wherein said exendin-4 compound is administered in a regimen which additionally comprises administration of said thiazolidinedione insulin sensitizer.

19. The method according to claim 1, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are co-administered.

20. The method according to claim 1, wherein said exendin-4 compound is a parenteral medicament.

21. The method according to claim 1, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are both in a single parenteral medicament.

22. The method according to claim 1, wherein said thiazolidinedione insulin sensitizer is an oral medicament.

23. The method according to claim 1, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are administered in suboptimal dosages.

24. The method according to claim 1, wherein the dosage of exendin-4 compound is from 1 μ g/day to 50 μ g/day.
25. The method according to claim 1, wherein the dosage of thiazolidinedione insulin sensitizer is from 0.01 mg/day to 10 mg/day.
26. The method according to claim 1, wherein the dosage of thiazolidinedione insulin sensitizer is from 0.1 mg/day to 3 mg/day.
27. The method according to claim 1, wherein the dosage of thiazolidinedione insulin sensitizer is less than 2 mg/day.
28. The method according to claim 1, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are administered in amounts and for a sufficient time to produce a synergistic effect.
29. The method according to claim 1, wherein said patient is a human.
30. A pharmaceutical composition comprising an exendin-4 compound, a thiazolidinedione and a pharmaceutically acceptable preservative.
31. The pharmaceutical composition according to claim 30, further comprising a buffer and an isotonicity agent.
32. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound is selected from the group consisting of exendin-4, an exendin-4 analogue, an exendin-4 derivative, an exendin-4 fusion protein, a DPPIV protected exendin-4, and an immunomodulated exendin-4.
33. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound has a binding affinity towards the GLP-1 receptor which is at least ten fold higher than that of GLP-1(7-37).

34. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound has a binding affinity towards the GLP-1 receptor which is at least 100 fold higher than that of GLP-1(7-37).

5 35. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound has at least the same affinity towards the GLP-1 receptor as that of exendin-4(1-39).

36. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound has at least twice the affinity as that of exendin-4(1-39) towards the GLP-1 receptor as
10 that of exendin-4(1-39).

37. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound is a fusion protein which comprises exendin-4, an analogue thereof or a derivative of any one of the foregoing, coupled optionally via a spacer to a stabilizing peptide which confers an increased half-life in human serum to said fusion protein as compared to the fusion
15 protein devoid of said spacer and stabilizing peptide.

38. The pharmaceutical composition according to claim 37, wherein said spacer is selected from the group consisting of a peptide so that said fusion protein can be directly produced by
20 recombinant DNA techniques, a peptide connected in either end in a way that said fusion protein cannot be produced directly by recombinant DNA techniques, a peptide comprising two amino acid residues and a non-peptide moiety

25 39. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound comprises a sequence of 25 amino acids which are identical to a sequence of 25 amino acids in human serum albumin.

40. The pharmaceutical composition according to claim 30, wherein said exendin-4 compound
30 comprises a polyethylene glycol moiety.

41. The pharmaceutical composition according to claim 32, wherein said immunomodulated exendin-4 has an immune response in humans which is less than that of exendin-4(1-39), said immune response being measured as the concentration of antibodies reactive to the ex-
35 endin-4 compound after 4 weeks of treatment of the patient.

42. The pharmaceutical composition according to claim 32, wherein said immunomodulated
exendin-4 has an immune response in humans which is less than 20% of the response of
exendin-4(1-39), said immune response being measured as the concentration of antibodies
5 reactive to the exendin-4 compound after 4 weeks of treatment of the patient.

43. The pharmaceutical composition according to claim 30, wherein said thiazolidinedione
insulin sensitizer is selected from the group consisting of troglitazone, ciglitazone, pioglitazone,
rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037, T174, and TZD
10 300512, 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-
2,4-dione or a salt thereof.

44. The pharmaceutical composition according to claim 30, wherein the concentration of said
exendin-4 compound is from 0.005mg/ml to 0.5mg/ml and the concentration of said thia-
15 zolidinedione insulin sensitizer is from 0.5mg/ml to 20mg/ml.

45. The pharmaceutical composition according to claim 30, wherein the concentration of said
exendin-4 compound is from 0.01mg/ml to 0.1mg/ml and the concentration of said thia-
zolidinedione insulin sensitizer is from 1mg/ml to 10mg/ml.
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46. A method for increasing the number or size of beta-cells in a subject or stimulating beta-
cell proliferation in a subject, said method comprising administering an effective amount of an
exendin-4 compound and an effective amount of a thiazolidinedione insulin sensitizer to said
subject.
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47. The method according to claim 46, wherein said exendin-4 compound is selected from
the group consisting of exendin-4, an exendin-4 analogue, an exendin-4 derivative, an ex-
endin-4 fusion protein, a DPPIV protected exendin-4, and an immunomodulated exendin-4 .

30 48. The method according to claim 46, wherein said exendin-4 compound has a binding af-
finity towards the GLP-1 receptor which is at least ten fold higher than that of GLP-1(7-37).

49. The method according to claim 46, wherein said exendin-4 compound has a binding af-
finity towards the GLP-1 receptor which is at least 100 fold higher than that of GLP-1(7-37).
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50. The method according to claim 46, wherein said exendin-4 compound has at least the same affinity towards the GLP-1 receptor as that of exendin-4(1-39).

51. The method according to claim 46, wherein said exendin-4 compound has at least twice
5 the affinity as that of exendin-4(1-39) towards the GLP-1 receptor as that of exendin-4(1-39).

52. The method according to claim 46, wherein said exendin-4 compound is a fusion protein which comprises exendin-4, an analogue thereof or a derivative of any one of the foregoing, coupled optionally via a spacer to a stabilizing peptide which confers an increased half-life in
10 human serum to said fusion protein as compared to the fusion protein devoid of said spacer and stabilizing peptide.

53. The method according to claim 52, wherein said spacer is selected from the group consisting of a peptide so that said fusion protein can be directly produced by recombinant
15 DNA techniques, a peptide connected in either end in a way that said fusion protein cannot be produced directly by recombinant DNA techniques, a peptide comprising two amino acid residues and a non-peptide moiety.

54. The method according to claim 46, wherein said exendin-4 compound comprises a se-
20 quence of 25 amino acids which are identical to a sequence of 25 amino acids in human serum albumin.

55. The method according to claim 46, wherein said exendin-4 compound comprises a poly-
ethylene glycol moiety.

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56. The method according to claim 47, wherein said immunomodulated exendin-4 has an immune response in humans which is less than that of exendin-4(1-39), said immune response being measured as the concentration of antibodies reactive to the exendin-4 compound after 4 weeks of treatment of the patient.

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57. The method according to claim 47, wherein said immunomodulated exendin-4 has an immune response in humans which is less than 20% of the response of exendin-4(1-39), said immune response being measured as the concentration of antibodies reactive to the exendin-4 compound after 4 weeks of treatment of the patient.

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58. The method according to claim 46, wherein said thiazolidinedione insulin sensitizer is selected from the group consisting of troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037, T174, and TZD 300512, 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a salt thereof.

59. The method according to claim 46, wherein the exendin-4 compound is exendin-4(1-39) and the thiazolidinedione insulin sensitizer is troglitazone, pioglitazone, 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiazolidine-2,4-dione, or a salt thereof.

60. The method according to claim 46, wherein said exendin-4 compound is administered in a regimen which additionally comprises administration of said thiazolidinedione insulin sensitizer.

61. The method according to claim 46, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are co-administered.

62. The method according to claim 46, wherein said exendin-4 compound is a parenteral medicament.

63. The method according to claim 46, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are both in a single parenteral medicament.

64. The method according to claim 46, wherein said thiazolidinedione insulin sensitizer is an oral medicament.

65. The method according to claim 46, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are administered in suboptimal dosages.

66. The method according to claim 46, wherein the dosage of exendin-4 compound is from 1 µg/day to 50 µg/day.

67. The method according to claim 46, wherein the dosage of thiazolidinedione insulin sensitizer is from 0.01 mg/day to 10 mg/day.

68. The method according to claim 46, wherein the dosage of thiazolidinedione insulin sensitizer is from 0.1 mg/day to 3 mg/day.

69. The method according to claim 46, wherein the dosage of thiazolidinedione insulin sensitizer is less than 2 mg/day.

70. The method according to claim 46, wherein said exendin-4 compound and said thiazolidinedione insulin sensitizer are administered in amounts and for a sufficient time to produce a synergistic effect.

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71. The method according to claim 46, wherein said patient is a human.